Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis

Anna F Glasier, Sharon T Cameron, Paul M Fine, Susan J S Logan, William Casale, Jennifer Van Horn, Laszlo Sogor, Diana L Blithe, Bruno Scherrer, Henri Mathe, Amelie Jaspart, Andre Ulmann, Erin Gainer

Summary

Background **Emergency contraception can prevent unintended pregnancies, but current methods are only effective if used as soon as possible after sexual intercourse and before ovulation. We compared the efficacy and safety of ulipristal acetate with levonorgestrel for emergency contraception.**

Methods **Women with regular menstrual cycles who presented to a participating family planning clinic requesting emergency contraception within 5 days of unprotected sexual intercourse were eligible for enrolment in this randomised, multicentre, non-inferiority trial. 2221 women were randomly assigned to receive a single, supervised dose of 30 mg ulipristal acetate (n=1104) or 1·5 mg levonorgestrel (n=1117) orally. Allocation was by block randomisation stratified by centre and time from unprotected sexual intercourse to treatment, with allocation concealment by identical opaque boxes labelled with a unique treatment number. Participants were masked to treatment assignment whereas investigators were not. Follow-up was done 5–7 days after expected onset of next menses. The primary endpoint was pregnancy rate in women who received emergency contraception within 72 h of unprotected sexual intercourse, with a non-inferiority margin of 1% point difference between groups (limit of 1·6 for odds ratio). Analysis was done on the efficacy-evaluable population, which excluded women lost to follow-up, those aged over 35 years, women with unknown follow-up pregnancy status, and those who had re-enrolled in the study. Additionally, we undertook a meta-analysis of our trial and an earlier study to assess the efficacy of ulipristal acetate compared with levonorgestrel. This trial is registered with ClinicalTrials.gov, number NCT00551616.**

Findings **In the efficacy-evaluable population, 1696 women received emergency contraception within 72 h of sexual intercourse (ulipristal acetate, n=844; levonorgestrel, n=852). There were 15 pregnancies in the ulipristal acetate group (1·8%, 95% CI 1·0–3·0) and 22 in the levonorgestrel group (2·6%, 1·7–3·9; odds ratio [OR] 0·68, 95% CI 0·35–1·31). In 203 women who received emergency contraception between 72 h and 120 h after sexual intercourse, there were three pregnancies, all of which were in the levonorgestrel group. The most frequent adverse event was headache (ulipristal acetate, 213 events [19·3%] in 1104 women; levonorgestrel, 211 events [18·9%] in 1117 women). Two serious adverse events were judged possibly related to use of emergency contraception; a case of dizziness in the ulipristal acetate group and a molar pregnancy in the levonorgestrel group. In the meta-analysis (0–72 h), there were 22 (1·4%) pregnancies in 1617 women in the ulipristal acetate group and 35 (2·2%) in 1625 women in the levonorgestrel group (OR 0·58, 0·33–0·99; p=0·046).**

Interpretation **Ulipristal acetate provides women and health-care providers with an effective alternative for emergency contraception that can be used up to 5 days after unprotected sexual intercourse.**

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National Health Service Lothian, Edinburgh, UK (Prof A F Glasier MD, S T Cameron MD); **Department of Reproductive and Developmental Sciences, University of Edinburgh, Edinburgh, UK** (Prof A F Glasier, S T Cameron); **Planned Parenthood of Houston and Southeast Texas, Houston, TX, USA** (P M Fine MD); **National Health Service Grampian, Aberdeen, UK** (S J S Logan MD); **Planned Parenthood of Greater Miami, Palm Beach and the Treasure Coast, West Palm Beach, FL, USA** (W Casale MD); **Planned Parenthood Association of Utah, Salt Lake City, UT, USA** (J Van Horn MD); **Planned Parenthood of North East Ohio, Akron, OH, USA** (L Sogor MD); **National Institute of Child Health and Human Development, Bethesda, MD, USA** (D L Blithe PhD); **Bruno Scherrer Conseil, Saint Arnoult en Yvelines, France** (B Scherrer PhD); **and HRA Pharma, Paris, France** (H Mathe MSc, A Jaspart MSc, A Ulmann MD, E Gainer PhD)

Correspondence to: Prof Anna F Glasier, Family Planning and Well Woman Services, NHS Lothian, Dean Terrace Centre, 18 Dean Terrace, Edinburgh EH4 1NL, UK **Anna.Glasier@nhslothian.scot.nhs.uk**

Introduction

Emergency contraception is available in more than 140 countries, and in nearly 50 countries is available without a doctor's prescription.[1] In most developed countries there is awareness of the option of emergency contraception.[2,3] However, despite improved knowledge and access, the intervention is underused in every setting investigated.[3,4] Efforts to enhance the effect of emergency contraception on abortion rates have concentrated on increasing uptake. Advanced provision, giving women a supply to keep at home, does increase use,[5] but increased use has not reduced rates of unintended pregnancies.[5–8]

Effectiveness of emergency contraception is estimated by calculating the number of pregnancies that might have occurred without use of the intervention.[9] These calculations are fraught with difficulties[10] and the effectiveness of emergency contraception has probably been overestimated.[11,12] The most widely used emergency contraceptive drug is levonorgestrel 1·5 mg given orally within 72 h of sexual intercourse.[12,13] Levonorgestrel acts by interfering with ovulation.[14] However, inhibition of ovulation occurs in only 50% of menstrual cycles and is most likely to occur when emergency contraception is given early in the cycle, at a time when risk of conception is low, and least likely to occur when given just before

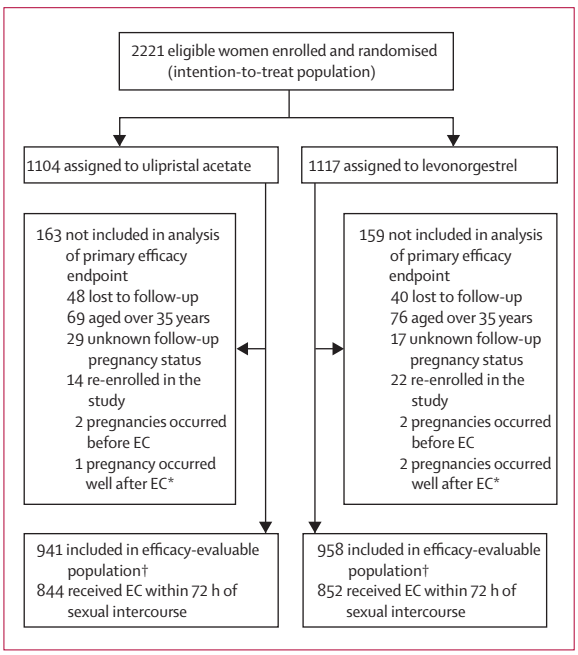

Figure 1: **Trial profile**
EC=emergency contraception. *At least 10 days after EC. †The efficacy-evaluable population was defined as women aged 35 years or younger who were enrolled for the first time in the study, and whose pregnancy status after treatment was known.

ovulation, when the probability of conception peaks.[14] Moreover, the efficacy of levonorgestrel declines with time after sexual intercourse, and there is only limited evidence that the drug is effective beyond 72 h after sexual intercourse.[13,15,16] Emergency insertion of a copper intrauterine device is effective after 72 h;[17] however, use is restricted by its availability and the need for insertion by a skilled health-care professional.

Although use of emergency contraception will always be limited by the ability of women to recognise or acknowledge that they have put themselves at risk of conception,[3,4] more pregnancies might be prevented by an orally active method that is more effective than levonorgestrel and works irrespective of the time of sexual intercourse in the menstrual cycle. Ulipristal acetate is a selective progesterone-receptor modulator that seems to be as effective as levonorgestrel for prevention of pregnancy when used within 72 h of unprotected sexual intercourse.[18] We assessed the efficacy and safety of ulipristal acetate compared with levonorgestrel when taken up to 120 h after sexual intercourse.

Methods

Participants

Study recruitment took place in 35 family planning clinics located in the UK, Ireland, and the USA. Women with regular menstrual cycles (24–35 days) seeking emergency contraception within 120 h of unprotected sexual intercourse were eligible for enrolment. Women were enrolled if they were aged 16 years or older in the UK and 18 years or older in the USA. Women who were pregnant, breastfeeding, sterilised, fitted with an intrauterine device, taking hormonal contraception, or whose partner was sterilised were excluded. Women who presented more than 72 h after sexual intercourse were initially offered an intrauterine device unless contraindicated. Upon enrolment, a urinary pregnancy test (level of detection 20 IU/L human chorionic gonadotropin [hCG]) was done and a blood sample taken and stored. All participants gave written informed consent and approval for the study was granted by all appropriate ethics committees in Europe and institutional review boards in the USA.

Randomisation and masking

Enrolled women were randomly assigned to receive ulipristal acetate 30 mg (HRA Pharma, Paris, France) or levonorgestrel 1·5 mg (Schering, Berlin, Germany) given orally. The randomisation schedule was stratified by site and time from unprotected sexual intercourse to treatment (within 72 h and 72–120 h) with a block size of four. The study was single blind—ie, participants were masked to treatment assignment, whereas those giving the interventions and study investigators were not, since the study drugs differed in appearance (different tablet size and blister pack). Study drug blister packs were packaged individually in identical opaque boxes labelled with a unique treatment number. After enrolment, the recruiting study investigator or research nurse registered each woman on a web-based electronic case record system (created and administered by Target Health, New York, NY, USA) and requested randomisation. Only after registration and request for randomisation did the system allocate a treatment number to the participant from the lot available on site, according to the randomisation schedule. The investigator or nurse took the appropriate treatment pack from storage, removed the tablet from the blister pack out of sight of the participant, and gave it to the participant under direct supervision.

Procedures

Throughout the study, women were asked to keep a daily diary to record further acts of sexual intercourse, contraceptive use, vaginal bleeding, concomitant medication, and adverse events. Women who needed to use emergency contraception in a subsequent menstrual cycle could re-enrol in the study.

Follow-up was done 5–7 days after expected menses. If menses had occurred and a pregnancy test was negative, participation ended. If menses had not occurred, participants returned a week later. Women with negative pregnancy tests but who had not menstruated were contacted every 2 weeks and periodic pregnancy testing was undertaken until return of menses or until 60 days after treatment when amenorrhoea was routinely investigated. Positive urinary pregnancy tests were

confirmed by measurement of serum β-hCG, and the pretreatment serum was assayed to verify whether pregnancy had occurred before treatment. Confirmed pregnancies were further assessed by serum quantitative hCG measurements and ultrasonography to estimate the date of fertilisation.

The primary efficacy endpoint was the rate of pregnancy in women who received emergency contraception within 72 h of unprotected sexual intercourse. The rate of pregnancy in women who received emergency contraception within 120 h of unprotected sexual intercourse was analysed as a secondary endpoint. Pregnancies and adverse events were assessed by a data safety monitoring board during the course of the study after completion of 400 and 1200 women and at study end. This board consisted of medical and clinical experts who were independent from the sponsor and the participating study sites. The board could apply stopping rules for efficacy or safety concerns, and reviewed every pregnancy (enrolment and follow-up serum hCG concentrations, ultrasound dating, menstrual cycle, and coital data) to establish whether conception clearly occurred before emergency contraception was given or well after treatment (at least 10 days after treatment). Pregnancies that met these criteria were deemed to be incompatible with treatment failure.

Statistical analysis

On the basis of results from a previous comparative trial,[18] we calculated that a sample size of 1654 women would be needed to reach at least 85% power to show non-inferiority of ulipristal acetate versus levonorgestrel when taken within 72 h of sexual intercourse. Taking into account additional women to be enrolled between 72 h and 120 h, and an anticipated rate of loss to follow-up of 10%, we planned to enrol 2044 women.

A non-inferiority analysis (ulipristal acetate *vs* levonorgestrel) was done with a logistic regression model with probability of conception as cofactor. In a large international multicentre trial,[19] levonorgestrel proved to be more efficacious than the Yuzpe method (ethinylestradiol 100 µg plus levonorgestrel 0·5 mg twice 12 h apart), with pregnancy rates of 1·1% in the levonorgestrel group and 3·2% in the Yuzpe group. A 1% point difference in pregnancy rates between two emergency contraceptive regimens was judged as not clinically relevant and was chosen as the non-inferiority margin for this trial. On the assumption of a pregnancy rate of 1·7% for levonorgestrel as reported in the previous comparative trial with ulipristal acetate,[18] the non-inferiority margin translates into a limit of 1·6 for an odds ratio (OR). Additionally, we compared the pregnancy rates and 95% CIs (calculated by use of the Agresti-Coull method[20]) for both treatment groups with the pregnancy rate expected in the absence of emergency contraception (calculated according to Trussell's method[9] with the pooled recognisable set of conception probabilities).

	Ulipristal acetate (n=1104)	Levonorgestrel (n=1117)
Age (years)	24·5 (6·1; 16·0–52·0)	24·9 (6·5; 16·0–55·0)
Age group (years)		
16–17	44 (4%)	49 (4%)
18–20	303 (27%)	279 (25%)
21–35	685 (62%)	706 (63%)
≥36	72 (7%)	83 (7%)
Ethnic origin		
White	804 (73%)	809 (72%)
Black	210 (19%)	207 (19%)
Asian	13 (1%)	21 (2%)
Other	77 (7%)	80 (7%)
Body-mass index (kg/m^2)	25·3 (5·9; 15·8–70·0)	25·2 (5·7; 14·9–53·7)
Smoking status		
Current smoker	399 (36%)	354 (32%)
Former smoker	142 (13%)	131 (12%)
Never smoked	563 (51%)	632 (57%)
Ever pregnant	522 (47%)	534 (48%)
Previous use of EC	606 (55%)	622 (56%)
Cycle length at screening (days)	28·7 (1·7; 24·0–35·0)	28·8 (1·7; 23·0–40·0)
Reason for requesting EC		
Condom failed	433 (39%)	430 (38%)
Other method failed	51 (5%)	70 (6%)
No contraception	620 (56%)	617 (55%)
Time from unprotected sexual intercourse to EC (h)		
0–24	367 (33%)	395 (35%)
25–48	388 (35%)	378 (34%)
49–72	238 (22%)	219 (20%)
73–96	72 (7%)	86 (8%)
97–120	38 (3%)	36 (3%)
>120	1 (<1%)	3 (<1%)
Episodes of unprotected sexual intercourse before enrolment		
1	987 (89%)	989 (89%)
2	83 (8%)	102 (9%)
>2	34 (3%)	26 (2%)

Data are mean (SD; range) or n (%). EC=emergency contraception.

Table 1: **Baseline characteristics of study participants (intention-to-treat population)**

The efficacy-evaluable population was defined as women aged 35 years or younger (as recommended by the US Food and Drug Administration[21]) who were enrolled for the first time in the study, and whose pregnancy status after treatment was known. Pregnancies judged by the data safety monitoring board to be incompatible with failure of emergency contraception were excluded from the analysis. Demographics and safety (frequency and intensity of adverse events and changes in menstrual cycle characteristics) were described for the intention-to-treat population. Serious adverse events were defined in accordance with the International Conference on Harmonisation E2 guidelines.[22] Statistical analyses were done with SAS version 8.2. This trial is registered with ClinicalTrials.gov, number NCT00551616.

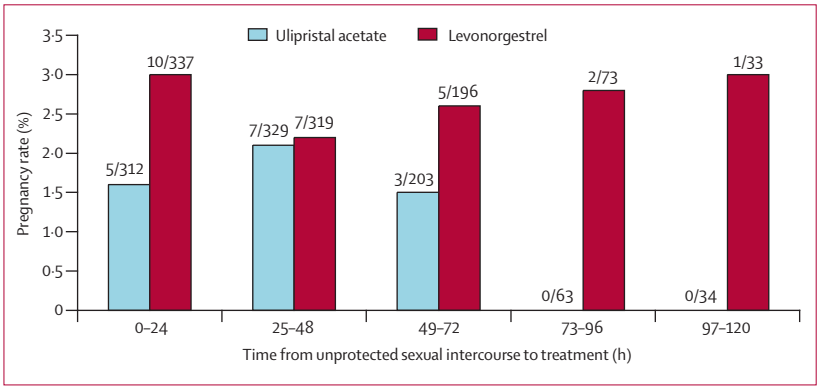

***Figure 2*: Pregnancy rates according to time from unprotected sexual intercourse to intake of emergency contraception (efficacy-evaluable population)**
n/N is shown at the top of each column.

Meta-analysis

To increase statistical power and provide better generalisability of results, we combined the data from this trial with those from the only available head-to-head comparison of ulipristal acetate with levonorgestrel, which was a similar study with respect to the design and method of assessment of the primary endpoint, but which enrolled women up to only 72 h after sexual intercourse.[18] The doses, formulations, and dosing regimens of the drugs in this earlier study, reported by Creinin and colleagues, differed from those used in our trial. The earlier study compared 50 mg ulipristal acetate formulated in a gelatine capsule with 0·75 mg levonorgestrel taken twice 12 h apart. The ulipristal acetate formulation used in our study was developed to reproduce the efficacy profile of the 50 mg capsule; micronisation of the drug allowed reduction of the dose from 50 mg to 30 mg when used in tablet form, and an indirect pharmacokinetic comparison confirmed the similarity of the two formulations.[23] Therapeutic equivalence of the two 0·75 mg and 1·5 mg levonorgestrel dosing regimens has been reported.[16]

Data from the efficacy-evaluable population in each study were pooled. A nominal logistic model was used to explain the occurrence of pregnancy with study and treatment included by constraint in the model as covariates. The significance of the following covariates was assessed in the model: participant's age, pregnancy history, body-mass index, time from unprotected sexual intercourse to treatment, Trussell's[9] probability of conception, time from unprotected intercourse to ovulation, and occurrence of further intercourse. Likelihood ratio tests were used to select confounding factors and test the treatment effect.

Apart from the study and treatment factors, only significant covariates were retained in the model. The magnitude of treatment effect was estimated from the model by the OR with 95% CIs. Analyses were done according to time from sexual intercourse to intake of emergency contraception (within 24 h, 72 h, or 120 h). Analyses were done with SAS Institute JMP version 4.

Role of the funding source

The sponsor of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Between April 9, 2007, and April 2, 2009, 2221 randomised women were treated with ulipristal acetate (n=1104) or levonorgestrel (n=1117). Only 88 women (4%) were lost to follow-up and they were similarly distributed between groups. The efficacy-evaluable population consisted of 1899 women, excluding those women lost to follow-up, those aged over 35 years (n=145), women with unknown follow-up pregnancy status (n=46), and those who re-enrolled in the study (n=36). Seven pregnancies judged by the data safety monitoring board to have occurred before emergency contraception was taken (n=4) or at least 10 days after treatment (n=3) were also excluded. In the efficacy-evaluable population, 1696 women received emergency contraception within 72 h after sexual intercourse, therefore exceeding the required sample size (n=1654) for the primary efficacy assessment. Table 1 shows baseline characteristics of study participants.

50 pregnancies occurred in the intention-to-treat population, 20 in the ulipristal acetate group and 30 in the levonorgestrel group (including the seven pregnancies that were judged as not compatible with treatment failure). In the efficacy-evaluable population, 37 pregnancies occurred in women who received emergency contraception within 72 h of sexual intercourse; there were 15 (1·8%, 95% CI 1·0–3·0) pregnancies in 844 women in the ulipristal acetate group and 22 (2·6%, 1·7–3·9) in 852 women in the levonorgestrel group (OR 0·68, 95% CI 0·35–1·31).

The pregnancy rate in both groups was significantly lower than the expected pregnancy rate (1·8% observed *vs* 5·5% expected for ulipristal acetate, p=0·001; 2·6% observed *vs* 5·4% expected for levonorgestrel, p=0·001). Efficacy results were consistent with those obtained for the intention-to-treat population (data not shown). Figure 2 shows the pregnancy rates in both groups over time. 203 women used emergency contraception between 72 h and 120 h after sexual intercourse (ulipristal acetate, n=97; levonorgestrel, n=106). All three pregnancies in the 72–120 h subgroup were in women in the levonorgestrel group. Significantly more pregnancies were prevented with ulipristal acetate than with levonorgestrel (p=0·037) in women who received emergency contraception between 72 h and 120 h after sexual intercourse. For the pregnancy rate in women who received emergency contraception within 120 h of sexual intercourse, the odds ratio was 0·57 (95% CI 0·29–1·09).

34 (68%) of the 50 pregnant women in the intention-to-treat population chose not to continue their pregnancy and opted for abortion (ulipristal acetate, n=14; levonorgestrel, n=20). Nine (18%) pregnancies ended in miscarriage (ulipristal acetate, four; levonorgestrel, five, including one molar pregnancy) and three (6%) pregnant women were lost to follow-up (ulipristal acetate, one; levonorgestrel, two). Four (8%) women decided to continue with their pregnancy, of whom one woman (ulipristal acetate) was lost to follow-up and three (levonorgestrel) delivered at term.

Adverse events were reported by 597 (54%) of 1104 women in the ulipristal acetate group and 626 (56%) of 1117 women in the levonorgestrel group. 1414 (94%) of 1506 events in the ulipristal acetate group and 1531 (94%) of 1629 in the levonorgestrel group were rated mild or moderate. The most frequently reported adverse events were similar for both groups (figure 3). Two serious adverse events were judged possibly related to use of emergency contraception; a case of dizziness in the ulipristal acetate group (resolved within 24 h) and the molar pregnancy in the levonorgestrel group. Adverse event profiles of women who re-enrolled more than once did not differ from those of the overall study population.

Onset of next menses after emergency contraception occurred a mean 2·1 days (SD 8·2) later than expected in the ulipristal acetate group and 1·2 days (7·9) earlier than expected in the levonorgestrel group (p=0·001), but duration of bleeding was not affected by emergency contraception. In women with available data on cycle length, menses occurred within 7 days of expected time in 769 (76%) of 1013 women in the ulipristal acetate group and in 731 (71%) of 1031 women in the levonorgestrel group.

The efficacy population in the trial by Creinin and colleagues[18] consisted of 1546 efficacy-evaluable women, in whom there were 20 pregnancies (table 2). Thus, in the combined dataset of 3445 women there were 60 pregnancies. Women in our trial were more likely to be younger (mean 23·6 years *vs* 24·3 years, p<0·0001), heavier (mean body-mass index 25·2 kg/m² *vs* 24·1 kg/m², p<0·0001) and to have waited longer to take emergency contraception after sexual intercourse (mean 39·7 h *vs* 35·3 h, p<0·0001) than were women in the trial by Creinin and colleagues.[18] The overall pregnancy rate in both groups combined was higher in our trial than in the earlier trial (40 of 1899, 2·1%, *vs* 20 of 1546, 1·3%). Despite these inter-study differences, which were taken into account in the analyses through stratification, the two treatment groups were well balanced in the combined dataset.

Upon meta-analysis of the two datasets combined, the rate of pregnancy was lower in the ulipristal acetate group than in the levonorgestrel group when emergency contraception was taken within 24 h, 72 h, or 120 h after sexual intercourse (table 2).

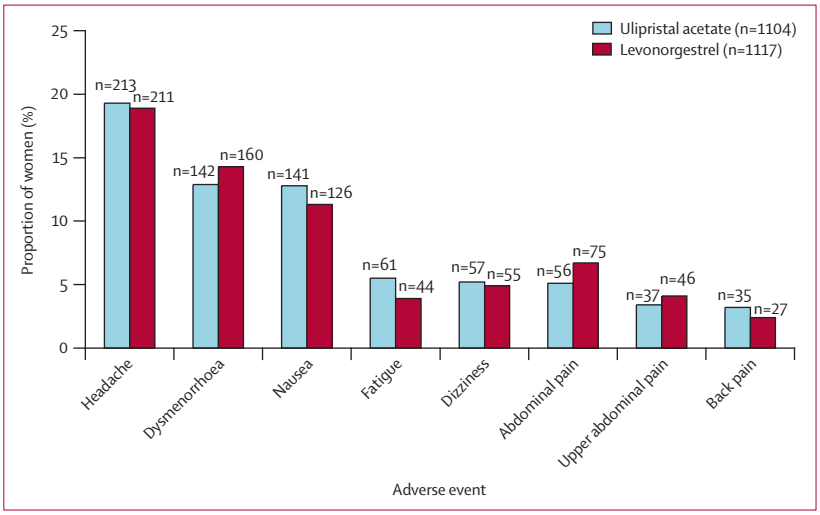

Figure 3: **Most frequent adverse events (intention-to-treat population)**

Discussion

Our trial shows that the selective progesterone-receptor modulator ulipristal acetate is non-inferior to levonorgestrel for emergency contraception. This finding accords with the results of an earlier trial in which ulipristal acetate was at least as effective as levonorgestrel when taken up to 72 h after sexual intercourse.[18] In both studies, ulipristal acetate seemed to prevent more pregnancies than did levonorgestrel, irrespective of the interval between sexual intercourse and treatment, or whether the intention-to-treat or efficacy-evaluable population was used for analysis. However, the difference between groups was not significant in either study, but neither study was powered to demonstrate superiority. Combination of data from the two studies allowed analysis of a sample sufficiently large to show that ulipristal acetate almost halved the risk of becoming pregnant compared with levonorgestrel in women who received emergency contraception within 120 h after sexual intercourse (OR 0·55, 95% CI 0·32–0·93). If emergency contraception was used within 24 h of unprotected sexual intercourse (when a third of participants in our study presented for emergency contraception), the risk of pregnancy was reduced by almost two-thirds compared with levonorgestrel (OR 0·35, 0·11–0·93).

The accepted effectiveness of levonorgestrel up to 72 h is based on the results of a trial undertaken by WHO in which levonorgestrel prevented 95% of expected pregnancies when taken within 24 h of sexual intercourse, 85% if taken within 25–48 h, and 58% if taken within 49–72 h.[12] In both trials of ulipristal acetate, levonorgestrel seemed to prevent fewer pregnancies than reported by WHO, in line with recent reports suggesting that the efficacy of levonorgestrel might be lower than expected.[24] The WHO trial was not done to the current rigorous standards for clinical research, excluded women who had more than one act of unprotected sexual intercourse

	Pregnancies, n/N (%)		Odds ratio (95% CI)*	p value*
	Ulipristal acetate	Levonorgestrel		
Creinin et al[18] (0–72 h)	7/773 (0·9%)	13/773 (1·7%)	0·50 (0·18–1·24)	0·135
Current study (0–120 h)	15/941 (1·6%)	25/958 (2·6%)	0·57 (0·29–1·09)	0·091
Meta-analysis (0–24 h)	5/584 (0·9%)	15/600 (2·5%)	0·35 (0·11–0·93)	0·035
Meta-analysis (0–72 h)	22/1617 (1·4%)	35/1625 (2·2%)	0·58 (0·33–0·99)	0·046
Meta-analysis (0–120 h)	22/1714 (1·3%)	38/1731 (2·2%)	0·55 (0·32–0·93)	0·025

*Inferential statistics based on the logistic regression model including significant covariates and the study factor.

Table 2: **Efficacy of emergency contraception in single studies and meta-analysis, according to time from unprotected sexual intercourse to intake of emergency contraception (efficacy-evaluable population)**

before enrolment, and did not include systematic pregnancy testing at follow-up. Moreover, the expected pregnancy rates without treatment in the WHO trial were higher than those used in our study because they were calculated by use of conception probabilities[25] that have since been updated to be more conservative.[11]

The only data suggesting a plausible mechanism of action for levonorgestrel describe an effect on ovulation.[14] Although levonorgestrel inhibits ovulation in 83% of menstrual cycles when given in the presence of a 12–14 mm ovarian follicle, this stage is early in the ovulatory process and the risk of conception in women with regular cycles is less than 30%.[26] By the time the follicle reaches 18–20 mm (and ovulation should occur within 48 h) and the probability of conception is over 80%, ovulation is prevented by levonorgestrel in only 12% of cycles (compared with 13% in the placebo group).[14] By contrast, when ulipristal acetate is given in the presence of a follicle measuring 18–20 mm, it prevents ovulation in 60% of cycles, therefore potentially preventing pregnancy in substantially more women than does levonorgestrel.[27] The ability of ulipristal acetate to inhibit ovulation even when it is given just before ovulation is particularly important because at this time in the cycle the probability of conception is at its peak and the frequency of sexual intercourse is at its highest.[9,28]

Progesterone-receptor modulators, including ulipristal acetate, given at high or repeated doses have an effect on endometrial histology and histochemistry that could theoretically impair implantation of a fertilised oocyte.[29,30] Although an endometrial effect, and therefore an additional postovulatory mechanism of action, cannot be excluded, the dose of ulipristal acetate used in this trial was specifically titrated for emergency contraception on the basis of inhibition of ovulation and might be too low to inhibit implantation.

The findings of our trial have limitations with respect to generalisability of the results to other delivery settings. The study was undertaken in family planning centres in countries where emergency contraception is now predominantly dispensed without prescription in pharmacies. Women were excluded if they were current or recent users of hormonal methods of contraception; however, emergency contraception is frequently used in women who have missed oral contraceptive pills. Furthermore, in this study women were advised to abstain from sexual intercourse or to use barrier methods for the remainder of the cycle. Increasingly, however, health-care providers advise women to start continuous hormonal contraception immediately after emergency contraception (a concept often referred to as bridging).[31] Future research will therefore be important to provide recommendations for the continuation or initiation of hormonal contraception after use of ulipristal acetate.

On the basis of this and other clinical trials that included a total of more than 4000 women,[18,23,32] in May, 2009, ulipristal acetate was approved by the European Medicines Agency as a safe and effective method of emergency contraception for use up to 5 days after unprotected sexual intercourse.[23] The drug is currently being launched throughout Europe. Ulipristal acetate seems to be as well tolerated as levonorgestrel and is associated with no greater risk of adverse events or menstrual disturbance. Additionally, data from women with various disorders treated with much higher doses of ulipristal acetate and other selective progesterone-receptor modulators suggest that these drugs are safe.[33] For women who presented on the fourth or fifth day after sexual intercourse in our trial, ulipristal acetate provided significant prevention of pregnancy whereas levonorgestrel did not, and, unlike levonorgestrel, ulipristal acetate is licensed for use beyond 72 h and up to 120 h. Although levonorgestrel might be offered by some health-care professionals to women who present late for emergency contraception, conclusive evidence of effectiveness is not available and use beyond 72 h is outside the terms of the product label. Mifepristone is only marketed for emergency contraception in China.[14] Insertion of an intrauterine device requires the availability of a skilled health-care professional, takes time, and involves an invasive and uncomfortable procedure. Therefore, even though such a device can provide long-lasting contraception, many women find it unacceptable.[34] In countries in which women know about emergency contraception, they know they need to use it as soon as possible (only 10% of women recruited to this study came for emergency contraception after 72 h), but we have no idea how many women simply do not bother to present for emergency contraception because they think they are too late. Moreover, in many countries around the world, the option of emergency contraception remains unknown to women, therefore extending the time limit for use is an important advance.

Ulipristal acetate is orally active and taken as a single dose. Since this drug seems no less effective than levonorgestrel, it provides women and health-care providers with an alternative choice for emergency contraception. The advantages of ulipristal acetate for policy makers are less clear. The risk of pregnancy after one act of sexual intercourse even at the most fertile time of the menstrual cycle is no more than 30%, so at least 70% of women who use emergency contraception are not

at risk. The estimated expected pregnancy rate in our trial was less than 6%, so arguably over 90% of participants did not need to use emergency contraception. The difficulty, however, is in identifying this small population of women. Since the safety of levonorgestrel has been proven by its use by millions of women in a variety of formulations and doses, the drug can be made available without prescription. Although ulipristal acetate could possibly be made available from pharmacies and nurses,[35] it cannot be made as easily accessible as levonorgestrel until there are more safety data. Health-care professionals might be tempted to recommend ulipristal acetate only to women who present after 72 h and those most at risk of pregnancy because they have had sexual intercourse mid-cycle. However, many women are unsure (or wrong) about the details of their menstrual cycle,[10] so this approach could lead to confusion and risk litigation if someone becomes pregnant after being given a method that is less effective but more easily accessible than ulipristal acetate. Thus, despite the issues around health-care service delivery, ulipristal acetate provides women and health-care providers with an alternative choice for emergency contraception that can be used up to 5 days after unprotected sexual intercourse.

Contributors

AFG was the chief investigator, wrote the first draft of both the protocol and report, and participated in data collection and data interpretation. AFG is the guarantor for the report. STC was the principal investigator at the Edinburgh site and participated in study design, data collection, and data interpretation. SJSL was the principal investigator at the Aberdeen site and participated in data collection, data verification, and data interpretation. PMF was the principal investigator/coordinator for the participating clinics in the USA and the principal investigator for Houston and southeast Texas and participated in data collection and interpretation. WC was the principal investigator in Greater Miami clinics and participated in data collection and data interpretation, JVH was the principal investigator in Utah clinics and participated in data collection. LS was the principal investigator in northeast Ohio clinics and participated in data collection and data interpretation. DLB participated in study design, data collection, and data interpretation. BS was the expert statistician and participated in the meta-analysis. HM was the initial trial coordinator, and wrote the first draft of both the protocol and report. AJ was the subsequent trial coordinator and participated in data collection and data analysis. AU and EG had the initial idea for the study, EG wrote the first draft of the protocol and report and participated in data analysis and data interpretation. All authors reviewed and approved the final version of the report.

Trial management

Trial management team: H Mathe, A Jaspart, E Gainer. *Data safety monitoring board:* J Trussell (chair), E Raymond, L Cheng, A Fisher. *Trial statistician:* L Ren. *Release recruitment sites (principal investigators): UK* Family Planning and Well Women Services, Edinburgh (S T Cameron); Square 13 Centre for Sexual and Reproductive Health, Aberdeen (S J S Logan); Sandyford Initiative, Glasgow (A Brown); Family Planning Centre, Palatine Center, Manchester (A Kasliwal); Central Abacus and Pace Young Abacus Bootle Health Centre (A Webb); Margaret Pyke Centre, London (J Stephenson); Contraception & Sexual Health Service, Victoria Health Centre, Nottingham (C Harper); Oxford PCT Community Health, Alec Turnbull Centre (C Porter); Brook Family Planning, Belfast (C Hunter). *Ireland* Well Woman Centre, Dublin (S McQuade). *USA* Planned Parenthood of Houston and Southeast Texas (P M Fine); Planned Parenthood Association of Utah (J Van Horn); Planned Parenthood of Texas Capitol Region (S Spear); Planned Parenthood of Northeast Ohio (L Sogor); Planned Parenthood of the Rocky Mountains (S Ginde); Planned Parenthood of Greater Miami (W Casale); Planned Parenthood of Los Angeles (D Nucatola).

Conflicts of interest

AFG, STC, and PMF have received lecture honorarium by HRA Pharma. BS has received consulting fees from HRA Pharma. HM, AJ, and EG are employees of HRA Pharma. AU has been an employee of and owns equity in HRA Pharma. SJSL, WC, JVH, LS, and DLB declare that they have no conflicts of interest.

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